

REMARKS

The pending claims of the present application were substantially copied from the claims of U.S. Patent Nos. 5,573,751 ("751 patent") and 5,409,688 ("688 patent") as part of a request for interference with the '751 and '688 patents. Since the '751 and '688 claims were held allowable and the pending claims of the present application have an earlier effective filing date than any of the '751 and '688 patent claims, the pending claims here should also be deemed allowable and an interference should be declared therebetween.

Claims 1-7, 9, 14, 16, 18, 19, 23 and 27 are pending in this application.

Claims 2 and 9 were rejected based on the term "an organic compound containing one or more carbon atoms and fluorine." Claims 1, 3-7, 14, 16, 18, 19, 23 and 27 were rejected under 35 U.S.C. § 112, ¶ 2 based on the term "freon". Applicants respectfully traverse.

The Examiner stated that all of the pending claims have an effective priority date of the instant application. Office Action, p. 6. Applicants respectfully traverse and submit that as established below, all of the pending claims have an effective filing date of April 2, 1990, the filing date of EP 90810262.7.

Additionally, claims 1-7, 9, 14, 16, 18, 19 and 23 were rejected under 35 U.S.C. §§ 102(e) and 103 as being anticipated and/or obvious in view of U.S. Patent No. 5,558,856 ("Klaveness"), U.S. Patent No. 5,776,429 ("Unger I"), U.S. Patent No. 5,585,112 ("Unger II"), U.S. Patent No. 5,558,094 ("Quay I") and U.S. Patent No. 5,393,524 ("Quay II"). Claims 1-7, 9, 14, 16, 18, 19 and 23 were further rejected under 35 U.S.C. §§ 102(e) and 103 as being anticipated and/or obvious in view of U.S. Patent No. 5,716,597 ("Lohrmann"). Applicants respectfully traverse.

Claims 1-6 were also rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent Nos. 5,088,499 ("Unger III"), 4,900,540 ("Ryan I") or 4,544,545 ("Ryan II") in view of U.S. Patent No. 4,265,251 ("Tickner") Applicants respectfully traverse.

Applicants thank the Examiner for the removal of the other previously cited references.

I. Applicants' Claims Satisfy 35 U.S.C. § 112

A. Substitutions Of Definitions Are Permitted

In Applicants' Amendment of March 16, 2001, Applicants amended claim 2 by substituting for "freon" in the limitation "a physiologically acceptable gas that is a freon" a well known and commonly accepted chemical definition for that class of compounds (*i.e.*, "physiologically acceptable gas that is an organic compound containing one or more carbon atoms and fluorine."). See Declaration Of Richard D. Chambers, ¶ 5, attached hereto as Exhibit 1¹. Therefore, Applicants' specification, which discloses "physiologically acceptable gases like freon" (*i.e.*, '889 specification, p. 15), conveys to one skilled in the art that Applicants had possession of the claimed "physiologically acceptable gas that is an organic compound containing one or more carbon atoms and fluorine."

Therefore, Applicants submit that claims 2 and 9 satisfy the written description requirement of 35 U.S.C. § 112, ¶ 1, and withdrawal of this rejection is respectfully requested.

Furthermore, claim 9 recites specific gases, and not the definition objected to in claim 2. Therefore, any analysis for written description of claim 9 must be made based on the language of claim 9, and not of claim 2. The '889 specification clearly recites the specific gases of claim 9. (*E.g.*, '889 specification, p. 52). Thus, for this additional reason, withdrawal of the rejection of claim 9 under this ground is respectfully requested.

¹ Applicants note that this Declaration was previously submitted in U.S.S.N. 09/115,963, which is the reissue application of the parent U.S. Pat. No. 5,413,774.

B. Applicants' Use Of Freon Is Proper

The Examiner rejected claims 1, 3-7, 14, 16, 18, 19, 23 and 27 under 35 U.S.C. § 112, ¶ 2 as allegedly being indefinite based on the claimed term "freon". At the outset, Applicants respectfully submit that each claim must be analyzed for compliance with 35 U.S.C. § 112, ¶ 2, and not simply rejected because the claim from which they depend was rejected. For example, a number of the above cited claims recite specific gases, and thus, cannot be indefinite under the Examiner's reasoning. Nevertheless, Applicants traverse and submit that the generic term "freon" is properly claimed and that the pending claims are definite under 35 U.S.C. 112, ¶ 2.

1. The Term "Freon" Is Well Understood In The Art

Applicants use the term "freon" to refer to the family of fluorinated carbon-containing compounds which have a distinctive set of characteristics. This family is well known and understood to those skilled in the art. Declaration Of Richard Chambers, ¶ 5 (Exhibit 1). Thus, the term "freon" is not indefinite and withdrawal of this rejection is respectfully requested.

Additionally, the term "freon" is used to refer to specific compounds that were disclosed to the public. This is not a case where a term is indefinite because it refers to some proprietary formula, secret process or unknown entity. The chemical structures of the freons were known and therefore this rejection should be withdrawn.

2. The United States Patent And Trademark Office
Has Acknowledged That A Claim To Freon Is Proper

Furthermore, the United States Patent And Trademark Office ("USPTO") has recognized and acknowledged the propriety of using the term "freon" by issuing claims in more than eight hundred patents which use this term. (Exhibit 2). A few representative claims of some recent patents issued by the USPTO which claim is reproduced below for the Examiner's convenience (*emphasis added*):

U.S. Pat. No. 6,300,369 - Hydroxy-kojic acid skin peel

37. The method of claim 36, wherein said degreaser is selected from the group consisting of alcohol, acetone, *freon* and chlorhexidine

U.S. Pat. No. 6,282,943 - Apparatus and method for detecting substances

13. The apparatus of claim 12, wherein the substance is a gas selected from the group consisting of natural gas, methane, propane, carbon monoxide, hydrogen sulfide, ethane, butane, oxygen, and *freon*.

U.S. Pat. No. 6,277,143 - Brain cooling apparatus and method for cooling the brain

5. The apparatus according to claim 4, wherein the compressed liquid is selected from the group consisting of carbon dioxide, *freon* and nitrogen.

U.S. Pat. No. 6,276,158 - Heat exchange equipment

15. Heat exchange equipment according to claim 1, in which the heat exchange fluid comprises a *freon*.

U.S. Pat. No. 6,123,523 - Gas-dispersion device

20. A method as defined in claim 18 wherein said gas is selected from the group consisting of argon, nitrogen and *freon*.

U.S. Pat. No. 5,988,438 - Apparatus for rapid inflation of inflatable object and related method

14. The inflator device according to claim 1, wherein the liquefied gas comprises at least one of a *freon*, a halon, nitrogen, or carbon dioxide.

Therefore, the USPTO has agreed, for over twenty five years (*i.e.*, since the 1976 issuance of U.S. Pat. No. 3,938,114), that the use of the term “freon” is well understood and does not make a claim indefinite. Thus, withdrawal of this rejection is respectfully requested.

We note that several claims containing the term “freon” have been analyzed by Courts but we are not aware of any case where a claim was held indefinite because of its use of the term “freon.”

3. The Use Of Generic Names Is Permissible

Additionally, generic names for chemicals are permissible for use in claims if their meanings are well-known and satisfactorily defined in the literature. The use of the term "freon" is used not only to refer to the refrigerants sold by DuPont, but is used generally by the art to refer to a well-known family of fluorinated carbon-containing compounds which have a distinctive set of characteristics. *Supra*, Section I.B.1. Thus, the use of the term "freon" is permissible in claims and withdrawal of this rejection is respectfully requested.

4. There Is No Objective Evidence To Support The Rejection

The Examiner argues that the use of the term "freon" in the claims renders them indefinite. However, the Examiner does not, and Applicants believe, cannot show any evidence in support. The Examiner cites to Freon-11, Freon-12 and Freon-114, all of which were undeniably known as freons as of Applicants' filing date. Thus, these freons do not support the rejection. Applicants are not aware of, nor has the Examiner cited, any chemicals that one skilled in the art would not have known was a freon. Therefore, this rejection should be withdrawn because it lacks an objective basis.

II. Effective Priority Date

Applicants respectfully submit that all of the pending claims have an effective filing date of April 2, 1990, the filing date of EP 90810262.7. Specifically, the Applicants have shown that Applicants had possession of the claimed invention, including the specific gases in the Applicants' dependent claims and the use of those gases with a surfactant for stabilizing the microbubbles:

1. The inventive concept of using CF₄, C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ was first disclosed in EP 90810262.7 by the term "freon" (*i.e.*, '262.7, p. 8). It is well known that CF₄,

C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ are freons. *See e.g.*, “‘Freon’ Fluorocarbons: Properties and Applications” in DuPont Technical Bulletin G-1 (E.I. duPont de Nemours and Company, Wilmington, DE), pp. 1-10 (1987). *Also*, Declaration of Richard Chambers, ¶¶ 4-5.

2. The inventive concept of using CF₄, C₄F₈, C₂F₆, C₂ClF₅, and C₃F₈ with a surfactant was first disclosed in EP 90810262.7 by the terms “freon” (*i.e.*, ‘262.7, p. 8) and “surfactants” (*i.e.*, ‘262.7, p. 5 “suspension being stabilized by the presence of the surfactants...”, p. 8 “surfactants which are convenient in this invention...”).

Thus, Applicants respectfully submit that the effective filing date of all of the pending claims in the instant application is April 2, 1990, the filing date of EP 90810262.7.

III. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Klaveness, Unger I, Unger II, Quay I and Quay II

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated by and obvious over Klaveness, Unger I, Unger II, Quay I and Quay II. Applicants respectfully traverse.

A. Klaveness Is Not Prior Art
To Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23

As explained above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Since Klaveness has a PCT publication date of July 22, 1993 and a 35 U.S.C. § 102(e) date of December 9, 1994, both of which are later than the effective filing date of the Applicants’ claims, Klaveness is not prior art to the Applicants’ claims. Thus, withdrawal of this rejection based on Klaveness is respectfully requested.

B. Unger I and Unger II Are
Not Prior Art To Schneider
Claims 1-7, 9, 14, 16, 18, 19, and 23

As stated above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7, which is prior to the earliest possible effective U.S. filing date of Unger I and Unger II. Applicants observe that both Unger I and Unger II mention some seven or more U.S. priority filing dates, most of which are continuation-in-part applications which continue to add new matter to each previous priority application. Yet the Examiner does not specify which of these dates is being relied upon in the Office Action. Applicants have determined that the earliest possible effective filing date under 35 U.S.C. 102(e) is April 30, 1993 for Unger I and November 30, 1993 for Unger II, and wish the Examiner to confirm this determination. Thus, withdrawal of this rejection based on Unger I and Unger II is respectfully requested.

C. Quay I and Quay II Are Not
Prior Art To Schneider
Claims 1-7, 9, 14, 16, 18, 19, and 23

As already discussed above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Thus, Quay I and Quay II, which have an earliest possible effective U.S. filing date of September 17, 1991, are not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Quay I and Quay II is respectfully requested.

D. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23 are
Nonobvious And Patentable Over Klaveness,
Unger I, Unger II, Quay I And Quay II

The Examiner rejected Schneider claims 1-7, 9, 14, 16, 18, 19 and 23 over Klaveness, Unger I, Unger II, Quay I and Quay II under 35 U.S.C. § 103. However, as explained above, none of Klaveness, Unger I, Unger II, Quay I or Quay II is prior art to the Schneider claims since

Klaveness, Unger I, Unger II, Quay I and Quay II all have earliest possible effective filing dates later than the April 2, 1990 effective filing date of Schneider's claims. Thus, withdrawal of this rejection in view of Klaveness, Unger I, Unger II, Quay I and Quay II is respectfully requested.

IV. Schneider Claims 1-7, 9, 14, 16, 18, 19, and 23
Are Patentable Over Lohrmann

The Examiner rejected claims 1-7, 9, 14, 16, 18, 19 and 23 under 35 U.S.C. §§ 102(e) and 103 as being anticipated by and obvious over Lohrmann. Applicants respectfully traverse.

As explained above, each of the pending claims of the instant application has an effective priority date of April 2, 1990, the filing date of EP 90810262.7. Since Lohrmann has an earliest possible effective filing date of June 4, 1993, which is later than the effective filing date of the Applicants' claims, Lohrmann is not prior art to the Applicants' claims. Thus, withdrawal of this rejection based on Lohrmann is respectfully requested.

V. Schneider Claims 1-6 Are Patentable
Over Unger III, Ryan I Or Ryan II In View Of Tickner

The Examiner rejected claims 1-6 under 35 U.S.C. § 103 as unpatentable over Unger III, Ryan I, or Ryan II in view of Tickner. The Examiner stated that one of ordinary skill in the art would have been motivated to use the freon gas disclosed in Tickner in the "gas filled microparticulate contrast agents" of Unger III, Ryan I or Ryan II. Office Action, p. 5. Applicants respectfully traverse.

The references relied upon by the Examiner fail to provide the necessary incentive or motivation to combine them in an attempt to create the Applicants' claimed invention. There is nothing in any of the references to suggest the desirability of the combination or modification in the manner indicated by the Examiner. Thus, the combination of references proposed by the Examiner is improper and Applicants respectfully request that this rejection be withdrawn.

1. There Is No Suggestion In The
Cited References To Combine

It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead one of ordinary skill in the art to combine those references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617-18 (Fed.Cir. 1999)(“Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.”)

Merely asserting that it would have been within the skill of the art to substitute one type of gas for another in the contrast agent of the primary reference is not enough. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed.Cir. 1988)(Holding that there was no support for the Examiner’s mere assertion that it would have been obvious to substitute one type of detector for another in the system of the primary reference); *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed.Cir. 1992)(Holding that there was no suggestion to combine a primary herbicide reference with secondary references directed to shampoo additives or byproducts of morpholines to arrive at the claimed invention.); MPEP § 2143.01.

There is nothing in any of the cited references to suggest the desirability of the combination or modification in the manner indicated by the Examiner. Specifically, there is no motivation or suggestion to combine Unger III, Ryan I or Ryan II with Tickner.

a. The Contrast Agent Used By Unger III,
Ryan I, Ryan II Are Completely Different From Tickner

There is no motivation to combine Unger III, Ryan I or Ryan II with Tickner because they are directed toward completely different types of contrast agents. Contrary to the Examiner’s argument, the mere fact that the contrast agents disclosed in Unger III, Ryan I, Ryan II and Tickner may be used for ultrasonic imaging does not make them the same as or analogous

to each other. Furthermore, as described below, the contrast agents of Unger III, Ryan I, and Ryan II all operate in a completely different manner from Tickner - the first three references relying on a bilayer liposome structure, and Tickner without any structure.

On the one hand, Unger III, Ryan I, and Ryan II all disclose contrast agent liposome structures made from, *inter alia*, phospholipid bilayers, which purportedly entrap gas or liquid for use as the "agent". The reported stability of these liposome structures are attributed to the arrangement of the phospholipids. They do not dissolve in the bloodstream to release free gas microbubbles nor can they be ground without destroying the structures themselves.

On the other hand, Tickner is directed to saccharide microparticle precursors which dissolve in the bloodstream to release free gas microbubbles which reflect the ultrasound signal and serve as the contrast agent:

It follows that a plurality of ultrasonic signals are generated as a function of time as the various microbubbles are formed on dissolving of the various particles 26 or on dissolving of portions thereof.

* * *

Briefly, as each microbubble is formed by dissolving of at least part of the wall 32 to expose the hollow space 30 or as the wall 32 thins sufficiently to cause the pressurized bubble 30 to fracture it, the microbubble expands beyond its equilibrium size, and alternately expands and contracts until it finally attains substantially its equilibrium size and shape. The frequency of the signal thereby detected by the transducer 34 is a function of the pressure in the cardiovascular system 12 opposite the positioning of the transducer 34.

Tickner, col. 4, lines 31-62. Figure 2 of Tickner illustrates the irregular reduction of the saccharide outer wall as it dissolves to release free gas microbubbles. These free gas microbubbles have no structure or envelope surrounding the gas. Additionally, Tickner recommends grinding to reduce the size and number of hollow spaces of the solid precursor microparticles. Tickner, col. 4, lines 11-14.

One of ordinary skill in the art thus will not be motivated to combine the non-dissolving, non-grindable contrast agent liposomes of Unger III, Ryan I, or Ryan II with the dissolving, grindable saccharide microparticles which release the free gas microbubble contrast agent of Tickner since they are directed toward completely different inventions.

b. Unger III, Ryan I And Ryan II
Teaches Away From Modification

Furthermore, Unger III, Ryan I And Ryan II all teach against the modification of their inventions or the combination of parts of their inventions with Tickner because Unger III, Ryan I And Ryan II assert that their agents are superior to all others, with no problems suggested or improvements needed. It is especially significant that despite the existence of the earlier Tickner references, Unger III, Ryan I and Ryan II chose not to incorporate or adopt Tickner's teaching regarding gases. The Examiner's proposed combination thus would not have been made by one of ordinary skill in the art.

In fact, Unger III specifically teaches away from combining with Tickner because Unger III distinguishes its liposome invention as being far superior to the prior art saccharine (*i.e.*, saccharide) "microbubbles":

Many of the prior art contrast agents developed to date for ultrasound have comprised liquids containing microbubbles of gas where the microbubbles have been encapsulated with gelatin or saccharine.

While the prior art has produced some ultrasound contrast agents which are echogenic on ultrasound, that is, provide a contrast enhancement signal, the contrast agents developed thus far have various problems...many of the methods for preparing these ultrasound contrast agents, particularly the gas encapsulated liposomes, are inefficient, expensive, and otherwise unsatisfactory.

Unger III, col. 2, lines 25-60. Such a distinction, by someone within the liposome art, of the saccharide art, excludes the use of Tickner in a rejection based on obviousness because it confirms that one of ordinary skill in the liposome art would not look into the saccharide art since it is “inefficient, expensive, and otherwise unsatisfactory.” *Id.*

Moreover, there are no road signs or blaze marks in the references that would lead one to ignore the bulk of their teachings and recommendations and be led to anything like Applicants’ specific stabilized microbubbles containing freon gas.

2. The Mere Fact That References Can Be
 Modified Or Combined Is Not Enough

Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-1784 (Fed. Cir. 1992)(emphasis added):

The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.

Thus, the mere fact that references can be combined or modified (and Applicants believe they cannot) does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed.Cir. 1990); MPEP § 2143.01. Hence, the Examiner’s attempt to combine the cited references alone without any suggestion in the references of the desirability of the modification is improper and should be withdrawn.

Contrary to the Examiner’s argument, the mere fact that there is some apparent overlap between the references based on the common disclosure of a gas such as air, which is disclosed in virtually every ultrasound imaging reference, does not serve as motivation or desirability for one skilled in the art to combine the references. As explained throughout this Response, the

references are still directed toward completely different types of contrast agents with completely different principles of operation.

3. The Modification Cannot Change
 The Principle Of Operation Of A Reference

The proposed modification cannot change the principle of operation of a reference. *In re Ratti*, 123 U.S.P.Q. 349 (C.C.P.A. 1959); MPEP § 2143.01. However, the Examiner's proposed modification would effectively change the principle of operation of each reference.

For example, Unger III, Ryan I, and Ryan II (liposomes) cannot be combined with Tickner (free gas microbubbles) because Unger III, Ryan I, and Ryan II explicitly rely on the benefits of a stabilizing bilayer of lipids surrounding the gas while Tickner relies on the benefits of a free gas bubble without any surrounding structure. Thus, these principles of operation are different and, contrary to the Examiner's argument, changing the type of material to encapsulate (or not encapsulate) the gas will change the principle of operation. Since the Examiner's proposed modification would thus improperly change the principle of operation of these references, withdrawal of this rejection is respectfully requested.

4. There Is No Reasonable
 Expectation Of Success

There also must be a reasonable expectation of success from the prior art in combining the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed.Cir. 1991). This motivation to combine and the reasonable expectation of success both must be found in the prior art and not the Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d at 1442. Using the Applicant's own disclosure in an obviousness analysis is considered improper and prohibited by case law. *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988)("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right

references in the right way so as to achieve the result of the claims in suit."); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.")

Since Unger III, Ryan I, and Ryan II are directed to vastly different types of contrast agents from Tickner (the first three with a structure, Tickner without), there is thus no reasonable expectation of success that Unger III, Ryan I or Ryan II may be combined with Tickner as suggested by the Examiner. This conclusion is supported by the assertion by each reference of its respective superiority over the other types of contrast agents and distinction from them.

Without any reasonable expectation of success, it is improper to combine the references cited by the Examiner and withdrawal of this rejection is respectfully requested.

5. Applicants Have Proven
 Unexpected Results

Proof of the superiority and nonobviousness of the Applicants' stabilized microbubble invention is explicitly disclosed in the examples of the specification. *See* Example 18. Applicants have even proven with experimental evidence that their claimed stabilized microbubbles have critical pressures nearly twice as great and have contrast durations nearly four times longer than the closest prior art gas of air (*i.e.*, stabilized microbubbles of air). *Id.*

With such proof of unexpected and superior results, Applicants' claimed invention is clearly nonobvious with respect to the cited references and the Examiner is respectfully requested to withdraw this rejection under 35 U.S.C. § 103. MPEP § 716.02(a).

VI. Response To Obviousness-Type Double Patenting
 And Provisional Obviousness-Type Rejections

Page 5 of the Office Action contains two rejections, the first alleging obviousness-type double patenting rejections over a listing of some 16 U.S. patents and the second alleging

obviousness-type double patenting over a host of pending patent applications. No "conflicting claims" were specified so it is difficult if not impossible to determine which of the patents and patent applications are of concern. As agreed to by the Examiner, these issues will be held in abeyance until claims are indicated to be otherwise allowable in this application.

If there are any further points requiring attention prior to allowance, the Examiner is asked to contact Applicant's counsel.

No fee is required. If there are additional fees, please charge them to our firm Deposit Account No. 14-1140.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Arthur Crawford", is written over a horizontal line.

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